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(54) Title: PRODRUG COMPOUNDS AND PROCESS FOR PREPARATION THEREOF

(57) Abstract: The compound of the invention is a prodrug form of a therapeutic agent linked directly or indirectly to an oligopeptide, which in turn, is linked to a stabilizing group. More generally, the present invention may be described as a new prodrug compound of a therapeutic agent, especially prodrugs comprising an antitumor therapeutic agent, displaying improved therapeutic properties relative to the products of the prior art, especially improved therapeutic properties in the treatment of cancerous tumors and/or in the treatment of inflammatory reactions such as rheumatic diseases. Improved therapeutic properties include decreased toxicity and increased efficacy. Particularly desired are prodrugs which display a high specificity of action, a reduced toxicity, an improved stability in the serum and blood, and which do not move into target cells until activated by a target cell associated enzyme. Prodrug compounds of a marker enabling tumors to be characterized (diagnosis, progression of the tumor, assay of the factors secreted by tumor cells, etc.) are also contemplated. The present invention also relates to the pharmaceutical composition comprising the compound according to the invention and optionally a pharmaceutically acceptable adjuvant or vehicle. Further, a method of decreasing toxicity by modifying a therapeutic agent to create a prodrug is disclosed. Several processes for creating a prodrug of the invention are described. Compounds of the invention include the prodrugs, Suc-ßAla-Leu-Ala-Leu-Dox, Suc-ßAla-Leu-Ala-Leu-Dnr, and Glutaryl-ßAla-Leu-Ala-Leu-Dox. Additionally intermediate compounds, important to the process of preparation of the prodrugs of the invention are claimed.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 05863 A (BAURAIN ROGER ;TROUET ANDRE (BE); UNIV LOUVAIN (BE); WALLONE REGIO) 29 February 1996 (1996-02-29) figures 3-5,8,11-13,16-22,25,28-32 examples ---	66,67
X	MASQUELIER, M. ET AL: "Incorporation and binding of anthracycline derivatives to low density lipoprotein: in vitro and in vivo studies on drug-LDL conjugates" RECENT ADV. CHEMOTHER., PROC. INT. CONGR. CHEMOTHER., 14TH, VOLUME ANTICANCER SECT. 1, PAGES 311-12. EDITOR(S): ISHIGAMI, JOJI. PUBLISHER: UNIV. TOKYO PRESS, TOKYO, JAPAN., XP000914544 page 311 ---	66,67

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 June 2000	28/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Dullaart, A

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	KING, H. DALTON ET AL: "Synthesis and proteolytic cleavage of 3'-N- peptidyl -adriamycin prodrugs" PEPT.: CHEM., STRUCT. BIOL., PROC. AM. PEPT. SYMP., 11TH, MEETING DATE 1989, PAGES 137-9. EDITOR(S): RIVIER, JEAN E.;MARSHALL, GARLAND R. PUBLISHER: ESCOM SCI. PUB., LEIDEN, NETH., XP000914543 figure 1 table 1 ---	66,67
X	EP 0 037 388 A (INST INT PATHOLOGIE CELLULAIRE) 7 October 1981 (1981-10-07) examples 2A,4.2 ---	66,67
Y	EP 0 475 230 A (BRUNSWICK CORP) 18 March 1992 (1992-03-18) page 4, line 39 - line 46 ---	66,67
Y	EP 0 640 622 A (DRUG DELIVERY SYSTEM INST LTD) 1 March 1995 (1995-03-01) page 13 ---	66,67
X	TROUET A ET AL: "A COVALENT LINKAGE BETWEEN DAUNORUBICIN AND PROTEINS THAT IS STABLE IN SERUM AND REVERSIBLE BY LYSOSOMAL HYDROLASES AS REQUIRED FOR A LYSOSOMOTROPIC DRUG CARRIER CONJUGATE IN-VITRO AND IN-VIVO STUDIES" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 1982, vol. 79, no. 2, 1982, pages 626-629, XP002029566 ISSN: 0027-8424 figure 2 table 1 page 629, left-hand column ---	66,67
X	UMEMOTO N ET AL: "PREPARATION AND IN-VITRO CYTOTOXICITY OF A METHOTREXATE-ANTI-MM46 MONOCLONAL ANTIBODY CONJUGATE VIA AN OLIGOPEPTIDE SPACER" INTERNATIONAL JOURNAL OF CANCER 1989, vol. 43, no. 4, 1989, pages 677-684, XP000120606 ISSN: 0020-7136 figure 1 page 681, right-hand column, last paragraph -page 682, left-hand column, line 4 page 682, right-hand column, line 13 - line 28 --- -/--	66,67

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 99/30393

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DE MARRE ANNE ET AL: "Evaluation of the hydrolytic and enzymatic stability of macromolecular Mitomycin C derivatives." JOURNAL OF CONTROLLED RELEASE 1994, vol. 31, no. 1, 1994, pages 89-97, XP000456583 ISSN: 0168-3659 figures 3,4 page 95, right-hand column -page 96, left-hand column	66,67
Y	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US MASQUELIER, M. ET AL: "Antitumor activity of daunorubicin linked to proteins: biological and antitumor properties of peptidic derivatives of daunorubicin used as intermediates" retrieved from STN Database accession no. 97:150635 HCA XP002139800 abstract & CURR. CHEMOTHER. IMMUNOTHER., PROC. INT. CONGR. CHEMOTHER., 12TH, VOL. MEETING DATE 1981, VOLUME 2, 1428-30. EDITOR(S): PERITI, PIERO;GIALDRONI GRASSI, GIULIANA. PUBLISHER: AM. SOC. MICROBIOL., WASHINGTON, D. C.,	66,67
Y	MASQUELIER, MICHELE ET AL: "Amino acid and dipeptide derivatives of daunorubicin. 1. Synthesis, physicochemical properties, and lysosomal digestion" J. MED. CHEM., 1980, VOL. 23, NO. 11, PAGE(S) 1166-70, XP000914522 abstract page 1167, paragraph RESULTS -page 1168	66,67
Y	WALDMANN H ET AL: "ENZYMATIC PROTECTING GROUP TECHNIQUES" CHEMICAL REVIEWS,US,AMERICAN CHEMICAL SOCIETY. EASTON, vol. 94, no. 4, 1 June 1994 (1994-06-01), pages 911-937, XP000450393 ISSN: 0009-2665 page 911, paragraph INTRODUCTION page 912, paragraph 2.1 -page 914	66,67
Y	WO 98 52966 A (CHRISTENSEN S BROGGER ;LILJA HANS (SE); DENMEADE SAMUEL R (US); IS) 26 November 1998 (1998-11-26) examples claims	67

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	ABOUD-PIRAK E ET AL: "CYTOTOXIC ACTIVITY OF DAUNORUBICIN OR VINDESINE CONJUGATED TO A MONOCLONAL ANTIBODY ON CULTURED MCF-7 BREAST CARCINOMA CELLS" BIOCHEMICAL PHARMACOLOGY 1989, vol. 38, no. 4, 1989, pages 641-648, XP000914578 ISSN: 0006-2952 page 642, right-hand column page 646, paragraph DISCUSSION -page 648 -----	66,67

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 67 in part, and 1-65

Present claims 1-65 relate to compounds, compositions and methods defined (inter alia) by reference to the following parameter(s):
P1: a therapeutic agent capable of entering a target cell
P2: a genetically-encoded or a non-genetically-encoded amino acid.
P3: a stabilizing group that hinders cleavage of said oligopeptide by enzymes present in whole blood.
P4: a linker group not cleavable by trouase.
The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.
It is further pointed out, that the enzyme trouase is not sufficiently characterised in the description. This insufficiency also leads to a lack of clarity within the meaning of Article 6 PCT and to a lack of disclosure within the meaning of Article 5 PCT, especially since the enzyme trouase has not been mentioned with this name previously in the databases Medline, Cancerlit, Chemical Abstracts, Embase or Biosis, nor in the patent literature.
Moreover, present claims 1-65 relate to an extremely large number of possible compounds, compositions and methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds, compositions and methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Also, present claims 1-65 relate to compounds, compositions and methods defined by reference to a desirable characteristic or property, namely "the compound being selectively cleaved by an enzyme associated with the target cell". The claims cover all compounds, compositions and methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds, compositions and methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds, compositions and methods by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.
Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claim 66, ant to those intermediates of claim 67, which are indeed intermediates in the synthesis of the compounds according to claim 66.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9605863 A	29-02-1996	BE 1008581 A	04-06-1996
		BE 1008580 A	04-06-1996
		AU 694546 B	23-07-1998
		AU 3248695 A	14-03-1996
		CA 2203622 A	29-02-1996
		EP 0769967 A	02-05-1997
		JP 10508291 T	18-08-1998
		NO 970748 A	10-04-1997
		NZ 291368 A	29-04-1999
		US 5962216 A	05-10-1999
EP 0037388 A	07-10-1981	BE 882541 A	16-07-1980
		DE 3167679 D	24-01-1985
		JP 1724800 C	24-12-1992
		JP 4009771 B	21-02-1992
		JP 57018624 A	30-01-1982
EP 0475230 A	18-03-1992	US 5155210 A	13-10-1992
		CA 2048094 A	12-03-1992
		JP 5294994 A	09-11-1993
EP 0640622 A	01-03-1995	US 5688931 A	18-11-1997
		CA 2134348 A	27-08-1994
		WO 9419376 A	01-09-1994
		JP 2610792 B	14-05-1997
WO 9852966 A	26-11-1998	AU 7582298 A	11-12-1998